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<b>(21) International Application Number:</b> PCT/US99/23173 <b>(22) International Filing Date:</b> 05 October 1999 (05.10.1999) <b>(30) Priority Data:</b> 09/166,236 05 October 1998 (05.10.1998) US <b>(60) Parent Application or Grant</b> THE REGENTS OF THE UNIVERSITY OF CALIFORNIA [/]; O. DARROW, Christopher, B. [/]; O. SATCHER, Joe, H., Jr. [/]; O. LANE, Stephen, M. [/]; O. LEE, Abraham, P. [/]; O. WANG, Amy, W. [/]; O. GRZYBICKI, Daryl, S. ; O.		<b>Published</b>
<b>(54) Title: IMPLANTABLE MEDICAL SENSOR SYSTEM</b> <b>(54) Titre: SYSTÈME DE DÉTECTEUR MÉDICAL IMPLANTABLE</b>  <b>(57) Abstract</b> <p>An implantable chemical sensor system for medical applications is described which permits selective recognition of an analyte using an expandable biocompatible sensor (16), such as a polymer, that undergoes a dimensional change in the presence of the analyte. The expandable polymer is incorporated into an electronic circuit component (14) that changes its properties (e.g., frequency) when the polymer changes dimension. As the circuit (14) changes its characteristics, an external interrogator (18) transmits a signal transdermally to the transducer (12), and the concentration of the analyte is determined from the measured changes in the circuit. This invention may be used for minimally invasive monitoring of blood glucose levels in diabetic patients. The sensor system may also be extended to applications outside the body where the interrogator transmits a signal remotely across a physical barrier.</p> <b>(57) Abrégé</b> <p>L'invention concerne un système de détecteur chimique implantable destiné à des applications médicales, ce système de détecteur (16) permettant de reconnaître sélectivement une substance à analyser grâce à un détecteur biocompatible expansible, tel qu'un polymère, qui subit un changement de taille en présence de la substance à analyser. Le polymère expansible est incorporé dans un composant de circuit (14) électronique dont les propriétés (par exemple la fréquence) changent lorsque le polymère change de taille. Lorsque les caractéristiques du circuit (14) changent, un dispositif d'interrogation (18) externe transmet un signal transdermique au transducteur (12), ce qui permet de déterminer la concentration de substance à analyser à partir des changements mesurés dans le circuit. La présente invention peut s'utiliser pour un contrôle à effraction minimale de taux de glucose dans le sang de patients diabétiques. Le système de détecteur peut également être utilisé pour des applications extérieures au corps, le dispositif d'interrogation transmettant à distance un signal au-delà d'une barrière physique.</p>		

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<p>(21) International Application Number: PCT/US99/23173 (22) International Filing Date: 5 October 1999 (05.10.99) (30) Priority Data: 09/166,236 5 October 1998 (05.10.98) US (71) Applicant: THE REGENTS OF THE UNIVERSITY OF CALIFORNIA [US/US]; 8th Floor, 1111 Franklin Street, Oakland, CA 94607-5200 (US). (72) Inventors: DARROW, Christopher, B.; 744 Mockingbird Lane, Pleasanton, CA 94566 (US). SATCHER, Joe, H., Jr.; 3909 Drakeshire Drive, Modesto, CA 95356 (US). LANE, Stephen, M.; 738 Stratford Road, Oakland, CA 94610 (US). LEE, Abraham, P.; 1428 Whitecliff Way, Walnut Creek, CA 94596 (US). WANG, Amy, W.; 2623 Ashby Avenue #2, Berkeley, CA 94705 (US). (74) Agent: GRZYBICKI, Daryl, S.; P.O. Box 808, L-703, Livermore, CA 94551 (US).</p>		<p>(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</p> <p><b>Published</b> <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p>
<p>(54) Title: IMPLANTABLE MEDICAL SENSOR SYSTEM</p> <div data-bbox="406 1134 1088 1491"></div> <p>(57) Abstract</p> <p>An implantable chemical sensor system for medical applications is described which permits selective recognition of an analyte using an expandable biocompatible sensor (16), such as a polymer, that undergoes a dimensional change in the presence of the analyte. The expandable polymer is incorporated into an electronic circuit component (14) that changes its properties (e.g., frequency) when the polymer changes dimension. As the circuit (14) changes its characteristics, an external interrogator (18) transmits a signal transdermally to the transducer (12), and the concentration of the analyte is determined from the measured changes in the circuit. This invention may be used for minimally invasive monitoring of blood glucose levels in diabetic patients. The sensor system may also be extended to applications outside the body where the interrogator transmits a signal remotely across a physical barrier.</p>		

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**Description**

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### IMPLANTABLE MEDICAL SENSOR SYSTEM

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The United States Government has rights in this invention pursuant to Contract No. W-7405-ENG-48 between the United States Department of Energy and the University of California for the operation of Lawrence Livermore National Laboratory.

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### BACKGROUND OF THE INVENTION

#### Field of the Invention

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5 The present invention relates to an implantable medical device for continuous, minimally invasive monitoring of a chemical analyte of interest using an expandable, biocompatible material incorporated into an electronic circuit component that is interrogated transdermally.

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#### Description of Related Art

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10 Various implantable medical monitoring devices have been developed to measure internal physiological conditions of a patient. For example, an implantable medical sensor that determines the oxygen content of blood using a light-emitting diode and a phototransistor is described in U.S. Patent No. 4,815,469 to Cohen *et al.*

15 U.S. Patent No. 5,709,225 to Budgifvars *et al.* describes a medical implant with a capacitive sensor, which is coated with a magnetically sensitive material that causes capacitance changes in the presence of a magnetic field.

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20 Some medical devices use sensors coupled with frequency tuned L-C circuits, where the sensor mechanically translates the changes in the physiological condition to the inductor or capacitor of the tuned L-C circuit. An external transmitter detects the resulting changes in resonant frequency of the circuit. For example, U.S. Patent

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No. 5,704,352 to Tremblay *et al.* describes an implantable passive biosensor for monitoring physiological conditions and converting the signals to digital format. In particular, the sensors are pressure transducers that detect the pressure of cerebrospinal fluid in the cavities of a patient's brain, which is useful for monitoring the operation of a cerebrospinal fluid shunt for treating hydrocephalus. U.S. Patent No. 4,114,606 to Seylar describes an implantable device useful for monitoring intracranial pressure for the treatment of hypertension. The resonant frequency of the passive L-C circuit implanted in the cranium varies with changes in intracranial pressure. An external monitor interrogates and detects the frequency changes in the pressure transducer. Neither of these patents describes specific mechanisms or devices for transducing other physiological conditions.

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The application of a transducer in an implantable medical device that reliably monitors changes in specific chemical analytes, such as blood glucose, would be advantageous. Blood glucose levels are of particular concern because diabetes is a chronic illness that affects more than 110 million people worldwide. Conventional therapy for the most severe form of diabetes, insulin-dependent diabetes mellitus (Type I), is to administer one or more injections per day of various forms of insulin, while monitoring blood glucose levels two or three times daily with commercial glucometers that require the withdrawal of blood samples. In practice, near normal blood sugar levels are difficult to maintain with this type of therapy due to the enormous inconvenience and day-to-day burden of conventional home-monitoring techniques. The resulting large fluctuations in blood glucose levels may be responsible for a number of serious secondary ailments commonly associated with diabetes, including stroke, liver and kidney damage, and loss of eyesight.

The present invention addresses the need for a convenient, minimally invasive medical sensor that provides continuous

5 measurements of an analyte of interest using an expandable,  
biocompatible material incorporated into an electronic circuit element.  
10 More specifically, this invention will help diabetic patients in  
monitoring blood glucose levels and achieving tighter blood glucose  
5 control without requiring blood samples to be drawn.

#### 15 SUMMARY OF THE INVENTION

The present invention provides an implantable sensor system  
for monitoring the concentration of a chemical analyte of interest.

20 The invention is used for medical applications, such as implanted  
sensor packages for long-term monitoring of physiological blood or  
10 tissue analytes, like glucose for control of diabetes. The analyte  
concentration is transduced by a circuit, the characteristics (e.g.,  
25 resonant frequency) of which are set by at least one circuit component  
(e.g., capacitance, inductance, resistance) whose value can be varied by  
the interaction between an analyte-sensitive material and the analyte.

15 For example, changing the distance between the plates with a glucose-  
30 swellable polymer can vary the capacitance of a parallel-plate capacitor.  
As the electrical characteristics of the circuit vary in response to  
changes in the concentration of the analyte, an external interrogator  
35 transmits a signal transdermally to the transducer, and the  
20 concentration of the analyte is determined from the response of the  
transducer to that signal.

40 It is an object of the present invention to provide an  
implantable sensor system to monitor one or more chemical analytes  
of interest, including ionic species and molecular species. It is also an  
25 object to provide an implantable transducer having a circuit that  
45 requires no internal source of power, and which incorporates an  
expandable material that changes its dimensions in the presence of the  
analyte to influence the properties of the transducer circuit. Another  
object of the invention is to provide a sensor system interrogated  
50 transdermally by an external device to measure the characteristics of

5 the circuit as the concentration of analyte changes. It is further an  
object of the invention to provide an implantable sensor system for  
10 monitoring the blood glucose levels in diabetic patients.

Although the medical applications are of particular interest, the  
5 present invention can also be used for sensing analytes outside the  
body or for non-medical sensing applications. Examples include the  
15 analysis of bodily fluids withdrawn from a patient, or for sensing  
across a barrier, such as a wall of a sealed container or a bioreactor. The  
present invention is useful for non-medical applications such as  
20 manufacturing processes associated with chemical, pharmaceutical, or  
food production. Thus, it is also an object of this invention to provide  
a non-implanted sensor to monitor one or more chemical analytes of  
25 interest using a transducer having a circuit that requires no internal  
source of power, and which incorporates an expandable material that  
15 changes its dimensions in the presence of the analyte to influence the  
properties of the transducer circuit. Another object of the invention is  
to provide a sensor system interrogated remotely by an external device  
30 to measure the characteristics of the circuit as the concentration of  
analyte changes. Other objects and advantages of the present  
20 invention will become apparent from the following description and  
accompanying drawings.

#### BRIEF DESCRIPTION OF THE DRAWINGS

40 The accompanying drawings, which are incorporated into and  
form part of this disclosure, illustrate embodiments of the invention  
and together with the description, serve to explain the principles of the  
25 invention.

45 **Figure 1** shows an implantable chemical sensor system  
according to the present invention.

**Figure 2** shows an embodiment of the present invention in  
50 which the transducer is a variable capacitor.



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Figure 3 shows an embodiment of the present invention in which the transducer is a variable inductor.

Figure 4 shows an embodiment of the present invention in which the transducer is a variable capacitor formed with a micro-electromechanical system.

Figure 5 shows the results of deformation measurements on an embodiment of the present invention.

Figure 6 shows a MEMS assembly configured to form the transducer according to the present invention.

Figure 7 shows a MEMS assembly fabricated by surface micromachining according to the present invention.

Figure 8 shows a MEMS assembly fabricated by surface micromachining according to the present invention.

Figure 9 shows a MEMS assembly fabricated by surface micromachining according to the present invention.

#### DETAILED DESCRIPTION OF THE INVENTION

The present invention is an implantable chemical sensor system for medical applications. The sensor system permits selective recognition of an analyte using an expandable biocompatible material, such as a polymer, which undergoes a dimensional change in response to changes in the concentration of the analyte of interest. The expandable polymer is incorporated into or mechanically connected to an electronic circuit element (e.g., capacitor, inductor, resistor) to cause a change in the value of that component, thereby altering the electrical characteristics of the circuit in a measurable way in response to changes in the analyte concentration. For example, changes induced in the value of a capacitor or inductor when the polymer changes dimension alter the resonant frequency of an L-C resonator circuit. Similarly, varying the value of a resistor leads to a measurable change in the R-C time constant of a discharging capacitor circuit.

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Changes in the electrical characteristics of the circuit are detected transdermally from outside the body using an electronic interrogation device and then analyzed to determine the concentration of the analyte. Examples of transdermal interrogation methods include (1) frequency dependent electromagnetic loading of an interrogator antenna by a passive resonator sensor circuit, and (2) audio monitoring of a tone chirped by the voltage of discharging R-C circuit. In medical applications, it is generally desirable to have the implanted sensor circuits powered externally by the interrogator circuit, although the sensor circuits may also be designed for passive interrogation or be powered by batteries.

Figure 1 shows a basic chemical sensor system according to the present invention. An implantable transducer package 10 includes a transducer circuit 12, which incorporates a circuit component 14 and a sensor 16 operably connected to the circuit component 14. A telemetry device 18 above the surface of the skin interrogates the implanted transducer circuit 12. The transducer package 10 is implanted subcutaneously, typically 2-4 mm below the surface of the skin, via a simple surgical procedure. The package 10 is miniaturized, typically about one centimeter in diameter. The implant comprises a biocompatible material that forms a hermetic (airtight) seal between the physiological environment and the electronic environment. The sensor circuit 12 may be mounted on a monolithic circuit board and contained within the hermetically sealed package 10.

Transduction of the analyte concentration is performed by the sensor 16, which maintains physical contact with the physiological environment while maintaining mechanical contact with at least one mechanically actuated circuit component 14 within the hermetically sealed package 10. The sensor 16 comprises a polymer that is designed (e.g., chemically altered) to undergo a (reversible) dimensional change (i.e., swelling, contraction) as the concentration of a selected analyte changes. Transduction occurs as a result of the mechanical action of

the dimensional change of the sensor 16 being transferred to the mechanically actuated circuit component 14, thereby leading to a change in the electrical characteristics of the circuit 12.

Variations in the electrical properties (e.g., resonant frequency) of the circuit 12 induced by changes in the analyte concentration are detected and may be processed by the telemetry device 18, which is positioned near the implanted transducer package 10. The telemetry device 18 could be connected to a drug delivery system, so that when the measured analyte concentration reaches a pre-determined level, the system responds to a signal from the device 18 by delivering a pre-determined dosage of medication to the patient. The sensor system of the present invention can also be expanded to incorporate multiple circuits and multiple sensors/transducers in a single package to detect more than one analyte simultaneously or sequentially.

The sensor system of the present invention can also be adapted for non-implanted, extracorporeal medical applications in which the chemical analyte is sensed outside the body. The present invention can be used for sensing across an impenetrable or impermeable barrier, such as a container having contents that include the analyte of interest.

Polymers that are responsive to certain analytes are known in the art. The analytes may be molecular species such as sugars (glucose), urea, ammonia, enzymes, or narcotic substances, or ionic species (electrolytes) such as hydrogen ions (pH), alkaline earth ions, alkali metal ions, or transition metal ions. For example, Kikuchi *et al.* (Anal. Chem., Vol. 68, No. 5, March 1996), describe a glucose-swelling hydrogel (poly(DMAA-co-MAPB-co-DMAA-co-BMA)-PVA) that undergoes a reversible volumetric expansion in response to a change in glucose concentration. A volumetric expansion as high as  $\Delta V/V=30\%$  occurs in response to a change of glucose concentration of

200 mg/dL. This corresponds to a linear dimensional swelling of  $\Delta r/r=10\%$ .

Referring to Figure 2, one embodiment of the invention is a subcutaneously implanted, biocompatible, hermetically sealed transducer package 20 containing a sensor circuit 22 that incorporates and is in electrical contact with a mechanically variable plate capacitor 24. The package 20 is formed to enclose the circuit 22 including the capacitor 24 and to create a housing for the sensor. In this embodiment, the housing is a pleated, expansible, bellows-shaped indentation or cavity 26 with a movable or deformable base 32. The bellows acts like a spring, with a reversible and predictable displacement for a given force. The axis of the bellows is normal to the surface of the package 20, and the cavity 26 may be several millimeters in diameter and approximately 1 mm deep. The cavity 26 is filled with an expandable polymer 28 and capped with a rigid, fine-pitch biocompatible material 30, such as a mesh, that allows perfusion of the polymer 28 by extracellular fluid, while mechanically constraining the analyte-sensitive polymer 28. As a result of this design, the swelling of the polymer 28 causes a measurable deflection of the base 32 of the bellows.

A planar conducting plate 34 is affixed to the deflectable or deformable base 32 of the bellows, and forms a parallel-plate capacitor with a second fixed planar conducting plate 36. Deflections of the base 32 of the bellows cause changes in the distance between the plates 34,36 of the capacitor, which results in an attendant change in capacitance. Some form of electrical connection, such as wire microbonds 38, connect the capacitor plates 34,36 to the circuit 22, so changes in the electrical properties of the circuit 22 are measured in response to changes in concentration of the analyte. Other configurations of the capacitor plates 34,36 in the transducer are possible, as long as the capacitance changes in response to the analyte-sensitive polymer. For example, the capacitor may comprise two fixed plates and a movable

5 dielectric, where the sensor and dielectric are connected such that the  
changes in dimensions of the sensor cause relative motion of the  
10 dielectric and the plates, causing the capacitance of the capacitor to  
change.

5 Referring to Figure 2, as the bellows 26 extends or contracts, the  
hermetic seal between the circuitry and the physiological environment  
15 is maintained. Variations in the electrical properties of the circuit 22  
induced by changes in the analyte concentration are detected by a  
telemetry device 39 that is positioned outside the body, but near the  
20 10 implanted transducer package 20. The device 39 determines the analyte  
concentration by remotely determining the properties of the circuit 22  
by evaluating a response of the transducer circuit obtained by  
electromagnetic, acoustic, or other means, to the applied interrogation  
25 signal. The results, having been read out transdermally, are presented  
15 on a display and archiving device, which can provide a continuous  
readout of the analyte concentration (e.g., mg/dL); the data may be  
recorded if desired (digital or analog format). The device 39 is  
30 preferably compact and portable, and may be a hand held device or  
worn on the body, like a wristwatch. Processing electronics within the  
20 device 39 may execute a stored program to evaluate and characterize  
35 the analyte-dependent data using known parameters of the transducer  
to determine the analyte concentration.

Referring to Figure 3, a second embodiment of the invention  
40 shows a subcutaneously implanted, biocompatible, hermetically sealed  
25 transducer package 40 containing a circuit 42 that incorporates and is in  
electrical contact with a mechanically variable inductor 44. The  
package 40 is formed to enclose the circuit 42 including the inductor 44  
45 and, as in Figure 2, create a bellows-shaped cavity 46 with a deformable  
base 48. The axis of the bellows is normal to the surface of the package  
30 40, and the cavity 46 may be several millimeters in diameter and  
approximately 1 mm deep. The cavity 46 is filled with an expandable  
50 polymer 50 and capped with a rigid, fine-pitch biocompatible plate or

5 mesh 52 that allows perfusion of the sensor polymer 50 by extracellular  
fluid, while mechanically constraining the analyte-sensitive polymer  
10 50. The expansion and contraction of the polymer 50 gives rise to a  
deflection of the base 48 of the bellows.

5 A disk 54 of magnetic material (e.g., ferrite) is affixed or in some  
manner connected to the deflectable or deformable base 48 of the  
15 bellows. The disk 54 forms an inductor 44 with a planar monolithic  
variable inductor coil 56, which is parallel to and in close proximity  
with the ferrite disk 54. Deflections of the base 48 of the bellows lead to  
20 10 changes in the distance between the disk 54 and the coil 56, which  
results in a change in the inductance of the inductor 44. The inductor  
44 is electrically connected to the rest of the circuit 42, for example, by  
wire microbonds 58; so changes in the electrical properties of the  
25 circuit 42 are measured in response to changes in concentration of the  
15 analyte. Other configurations of the magnetic disk 54 and inductor coil  
56 in the transducer are possible, as long as the inductance changes in  
response to the analyte-sensitive polymer.  
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As the sensor 50 changes dimensions, the hermetic seal between  
the circuitry and the physiological environment is maintained.

20 Variations in the electrical properties of the circuit 42 induced by  
changes in the analyte concentration are detected by a telemetry device  
35 59, such as that described for Figure 2. The device 59 is positioned  
outside the body, but near the implanted transducer 40, and  
determines the analyte concentration by remotely determining the  
40 25 properties of the circuit by evaluating a response of the transducer  
circuit obtained by electromagnetic, acoustic, or other means, to the  
applied interrogation signal. The results, having been read out  
45 transdermally, are presented on a display and archiving device, which  
can provide a continuous readout of the analyte concentration and  
30 record these data if desired. The telemetry device 59 may also be  
connected to a drug delivery system.  
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Referring to Figure 4, another embodiment of the invention is a subcutaneously implanted, biocompatible, hermetically sealed transducer package 60 containing a sensor circuit 62 that incorporates and is in electrical contact with a mechanically variable plate capacitor 64. The package 60 is formed to hermetically enclose the circuit 62 including a micro electro-mechanical system (MEMS) transducer device 66. The MEMS device comprises a micromachined well 68 filled with an expandable polymer 70 that swells or shrinks in the presence of the analyte of interest. The MEMS device may be made of silicon or another biocompatible material. The well 68 is bonded to and capped by a rigid, analyte-permeable grid chip 72 or retaining plate to mechanically constrain the polymer 70 in the well 68.

The well 68 may be formed by etching a silicon wafer 84, the opposite side of which has been deposited with a layer 74 of superelastic conductive material, for example, a metal such as  $\text{Ni}_x\text{Ti}_x$ . The etching process results in a well with a depth equal to the thickness of the silicon wafer. The conductive (metallic) layer 74 that remains after etching forms an elastic, deformable membrane 76 or diaphragm at the bottom of the well, which further serves as a hermetic seal between the physiological environment outside the package (on the polymer side of the membrane) and the electronic environment inside the package. Expansion (or contraction) of the sensor 70 gives rise to displacement or deflection of the membrane 76. The conductive layer 74 forming the deformable membrane 76 serves as one plate of the capacitor 64 and can extend only the length of the membrane 76, or beyond (as shown) if desired.

Figure 5 shows the results of deformation measurements on a mechanical prototype of the embodiment shown in Figure 4. In this example, optical profilometry was used to demonstrate the extent of deflection (about  $30\mu\text{m}$ ) of the membrane ( $4.0\text{mm} \times 4.0\text{mm}$ ) in response to swelling of a P-HEMA hydrogel polymer by an ionic solution to which the polymer was exposed. The membrane was

5 formed of a nickel titanium alloy ( $\text{Ni}_x\text{Ti}_x$ ). The superelastic properties  
of  $\text{Ni}_x\text{Ti}_x$  make the alloy a preferred material for the deformable  
10 membrane, although other alloys could be used to optimize the  
mechanical properties.

5 To complete the capacitor 64, a second planar conductive  
material is needed. Figure 4 shows a possible configuration; a second  
15 silicon or glass wafer 80 is etched to form a well-defined recess, and a  
conductive (metallic) coating 82 is deposited on the bottom of the  
recess. The wafers 82,84 can be bonded together to form a parallel plate  
20 capacitor with a defined capacitor gap, where the capacitance is  
determined by the separation of the flexible membrane 76 and the  
conductive coating 82. The capacitor 64 is connected to the circuit 62,  
such as by wire microbonds 86 or by direct integration of the circuit. In  
25 an alternative embodiment of the invention, the deformable  
15 membrane MEMS actuator device can be configured to form a variable  
planar inductor (as in Figure 3), instead of a capacitor.

30 As the sensor 70 changes dimensions and displaces the  
membrane 76, the seal formed by the membrane 76 between the circuit  
62 and the physiological environment is maintained. Variations in  
20 the electrical properties of the circuit 62 induced by changes in the  
35 analyte concentration are detected by a telemetry device 88 that is  
positioned outside the body, but near the implanted transducer 60.  
The interrogation device 88 determines the analyte concentration by  
remotely determining the properties of the circuit by evaluating a  
40 response of the transducer circuit obtained by electromagnetic,  
25 acoustic, or other means, to the applied interrogation signal.  
Processing electronics within the device 88 may execute a stored  
45 program to evaluate and characterize the analyte-dependent data using  
known parameters of the transducer to determine the analyte  
30 concentration. The results are read out transdermally and presented  
on a display and archiving device, which can provide a continuous  
50 readout of the analyte concentration and record these data if desired.



5 This remote interrogation feature is useful not only for medical  
implants, but for any sensing that must be performed across a physical  
10 barrier, or in situations in which physical contact with the  
sensor/actuator is not practical or possible.

5 Further integration of the variable circuit component with the  
other required circuit elements for a variable capacitor MEMS sensor,  
15 such as depicted in Figure 6, may be advantageous from a  
manufacturing standpoint. The MEMS-based capacitor (or inductor)  
can be directly fabricated on a wafer (or wafers) with other required  
20 circuit components, to form an integrated, MEMS-based implantable  
transducer circuit.

Figure 6 illustrates an embodiment of an integrated MEMS  
assembly formed from two subassemblies 101,102. The first (lower)  
25 subassembly 101 comprises a well 104 filled with an analyte-sensitive  
polymer that expands and contracts in response to the analyte. A rigid  
15 retaining mesh 103 allows permeation of the polymer by the analyte-  
containing fluid. A flexible, deformable conductive membrane 105 is  
patterned on the top surface 112 facing the second (upper) subassembly  
30 102. Also patterned on this top surface 112 is a planar inductor coil 106  
that is electrically connected to the movable capacitor membrane 105  
20 on the first subassembly 101 and to a fixed capacitor plate 107 on the  
second subassembly 102. Electrical contact from the coil 106 to the  
movable capacitor membrane 105 can be made through a patterned  
35 trace 108. Electrical contact to the fixed plate 107 can be made by a  
conductive via 109 that connects a first (lower) subcircuit pad 110 and a  
40 second (upper) subcircuit pad 111. The pads 110,111 are connected  
upon assembly of the first and second subassemblies 101,102, thereby  
45 completing the L-C circuit of this embodiment.

Figure 7 illustrates an alternative configuration of Figure 4,  
30 where the opposing electrode (capacitor plate) is surface  
micromachined instead of bulk micromachined and bonded. By  
50 polysilicon surface micromachining, an opposing electrode can be

integrated on the opposite side of the flexible membrane through a batch process, resulting in lower cost and smaller size of the overall device. This type of design will also provide a much smaller gap (<1000Å) for higher measurement sensitivity.

The fabrication process includes the low pressure vapor deposition of a silicon nitride layer 122 and patterning of grounding feedthroughs 124. A silicon nitride membrane 126 is then formed by patterning and anisotropically etching from the backside of the silicon substrate 120. A thin film 128 shape memory alloy (SMA) (e.g., Ti-Ni) is deposited on the front side to enhance toughness of the silicon nitride membrane 126. Electrical feedthrough from the SMA film 128 to the ground substrate 120 is established through the silicon nitride opening 124. A second silicon nitride layer 130 with a thickness of 100Å-1000Å is deposited on top of the SMA film 128 for insulation between the opposing electrode layers 128 and 132. A polycrystalline silicon layer 132 is deposited over a sacrificial SiO<sub>2</sub> layer 134 to form the top electrode. The sacrificial layer 134 (e.g., SiO<sub>2</sub> or glass), with a thickness of about 0.5µm to 2µm, is deposited on top of the silicon nitride layer 130 and patterned to form the gap 134 between the electrodes 128,132. The sacrificial layer 134 is later selectively etched away with etchants such as buffered hydrofluoride.

Figure 8 is an embodiment of the present invention that relies on inductance change rather than capacitance change and utilizes the same fabrication techniques as in Figure 7. In this embodiment, a spiral thin film metal inductor 140 is patterned on the top electrode 142. A hole 144 is patterned in the top electrode 142, and a pedestal 146 made of a magnetic material is patterned on the insulating nitride layer 148. The insulating layer 148 overlays the flexible membrane 150 and its support layer 152. When the membrane 150 moves in response to dimensional changes of the analyte-sensitive polymer (not shown), the pedestal 146 patterned on top of the moving membrane moves through the inductor coil 140, causing an inductance change. The

5 change in inductance is then detected by an external telemetry device,  
as described previously.

10 **Figure 9** is another capacitive sensing configuration fabricated  
using surface micromachining techniques. This embodiment includes  
5 moving comb pedestals 160 that are patterned on top of the moving  
membrane 162. The pedestals 160 are situated to move through static  
15 comb fingers 164 that are isolated from the movement of the  
membrane 162. As the pedestals 160 move through the fingers 164, the  
capacitive change (and therefore displacement of the moving  
20 membrane 162) is detected. The pedestals 160 and fingers 164 are made  
of conductive material, such as polysilicon or a metal (e.g., Al, Au).  
The advantage of this configuration is that the capacitance change is  
proportional to displacement and independent of the position. This  
25 simplifies the circuitry design from the parallel plate configuration of  
15 **Figure 7**.

30 The foregoing description of preferred embodiments of the  
invention is presented for purposes of illustration and description and  
is not intended to be exhaustive or to limit the invention to the  
precise form disclosed. Many modifications and variations are  
35 20 possible in light of the above teaching.

**Claims**

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THE INVENTION CLAIMED IS

1. A chemical sensor system for measuring the concentration of an analyte of interest, comprising:
  - a sensor, comprising a material that selectively responds to an analyte of interest by changing its dimensions;
  - a transducer, comprising an electronic circuit having at least one variable electrical characteristic that changes in response to dimensional changes of the sensor; and
  - a telemetry device that interrogates the transducer remotely across a physical barrier to measure the changes in the electrical characteristic of the circuit as the concentration of analyte changes.
2. The sensor system as recited in Claim 1, wherein the circuit comprises at least one mechanically actuated circuit component, wherein the dimensional changes of the sensor are used to mechanically actuate changes in the electrical characteristic of the circuit component.
3. The sensor system as recited in Claim 2, wherein the circuit component comprises a variable capacitor.
4. The sensor system as recited in Claim 3, wherein the capacitor comprises two plates, wherein at least one plate moves relative to the other in response to the sensor changing its dimensions.

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5. The sensor system as recited in Claim 4, wherein the transducer further comprises an area that moves in response to the sensor changing dimensions and that is connected to at least one plate.

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6. The sensor system as recited in Claim 1, wherein the transducer further comprises a housing for the sensor, including an area that moves in response to the sensor changing dimensions, and including a rigid, analyte-permeable material that constrains the sensor in the housing.

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7. The sensor system as recited in Claim 1, wherein the transducer is implantable and the telemetry device interrogates the transducer transdermally.

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8. The sensor system as recited in Claim 3, wherein the capacitor comprises two fixed plates and a movable dielectric, wherein changes in dimensions of the sensor cause relative motion of the dielectric and the plates, whereby the capacitance of the capacitor changes.

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9. The sensor system as recited in Claim 2, wherein the circuit component comprises a variable inductor.

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10. The sensor system as recited in Claim 9, wherein the inductor comprises an inductance coil, and the coil's inductance changes in response to the sensor changing its dimensions.

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11. The sensor system as recited in Claim 10, further comprising a magnetic material that moves in response to the sensor changing its dimensions.

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12. The sensor system as recited in Claim 9, wherein the inductor comprises an inductance coil and a magnetic material, wherein at least one of the coil and magnetic material move relative to the other, and the coil's inductance changes in response to the sensor changing its dimensions.

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13. The sensor system as recited in Claim 1, wherein the sensor comprises a polymer capable of reversibly expanding and contracting in volume in the presence of the analyte.

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14. The sensor system as recited in Claim 1, wherein the sensor comprises a hydrogel that changes dimensions in the presence of glucose.

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15. The sensor system as recited in Claim 1, wherein the sensor responds to at least one analyte selected from the group consisting of sugars, urea, ammonia, hydrogen ions, alkaline earth ions, alkali metal ions, transition metal ions, enzymes, and narcotic substances.

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16. The sensor system as recited in Claim 2, wherein the circuit component comprises a micro electromechanical system (MEMS) device.

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17. The sensor system as recited in Claim 16, wherein the MEMS device comprises a cavity into which the sensor is situated, and a flexible conductive membrane covering a portion of the cavity such that the membrane moves in response to the sensor changing its dimensions.

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18. The sensor system as recited in Claim 17, wherein the transducer includes a planar conductive material, wherein the planar material

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and the membrane comprise plates of a capacitor, wherein the capacitor's capacitance changes in response to the sensor changing its dimensions.

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19. The sensor system as recited in Claim 18, wherein the planar conductive material is deposited on a surface of an etchable substrate.

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20. The sensor system as recited in Claim 19, wherein a well is formed on the surface of the substrate, and the conductive material is deposited thereon.

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21. The sensor system as recited in Claim 17, wherein the MEMS device comprises at least one variable circuit component comprising a variable capacitor, the capacitance of which varies in response to deflections of the membrane.

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22. The sensor system as recited in Claim 21, wherein the MEMS device further comprises an integrated inductor.

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23. The sensor system as recited in Claim 17, wherein the MEMS device comprises at least one variable circuit component comprising a variable inductor, wherein the inductor comprises an inductor coil and a magnetic material that moves with the membrane.

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24. The sensor system as recited in Claim 1, wherein the circuit comprises a micro electromechanical system (MEMS) device which further comprises at least one variable circuit component co-fabricated with other circuit elements to form an integrated MEMS assembly.

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25. The sensor system as recited in Claim 1, wherein telemetry device measures the resonant frequency of the transducer circuit.

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26. The sensor system as recited in Claim 1, wherein telemetry device measures an acoustic tone, the frequency of which is moderated by the transducer circuit.

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27. A method for measuring the concentration of an analyte of interest using a sensor system, comprising:

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providing a transducer, comprising an electronic circuit and a sensor, wherein the sensor comprises a material that selectively responds to an analyte of interest by changing its dimensions, and wherein the circuit has at least one variable electrical characteristic that changes in response to dimensional changes of the sensor;

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placing the transducer in contact with the analyte; and

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providing a telemetry device that interrogates the transducer remotely across a physical barrier to measure the changes in the electrical characteristic of the circuit as the concentration of analyte changes.

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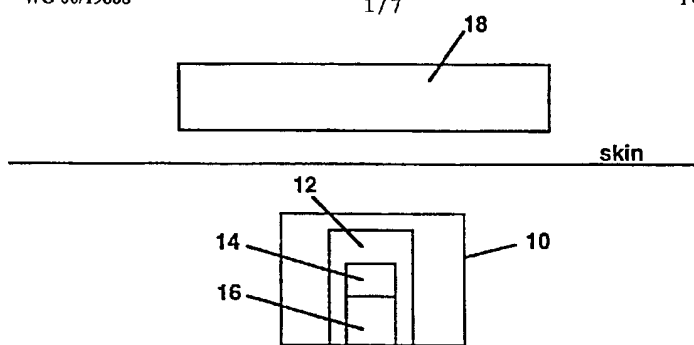


FIGURE 1

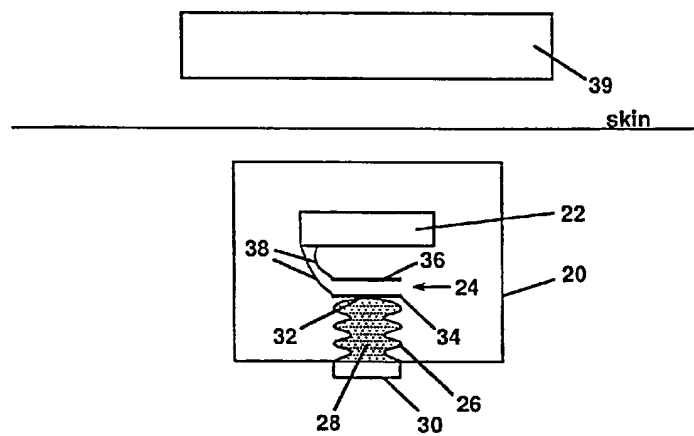
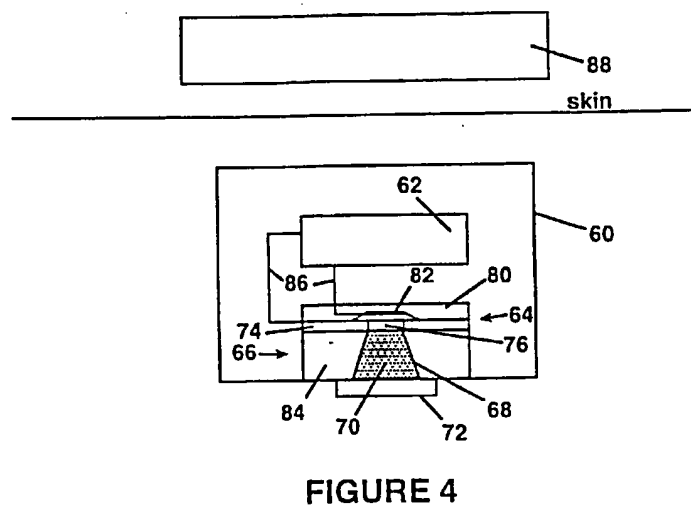
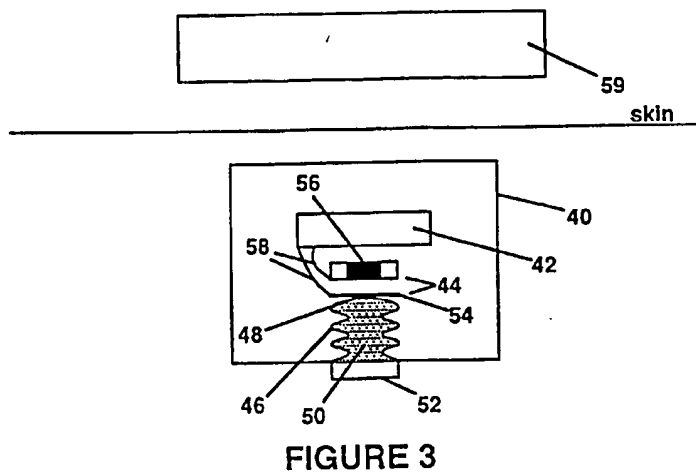


FIGURE 2



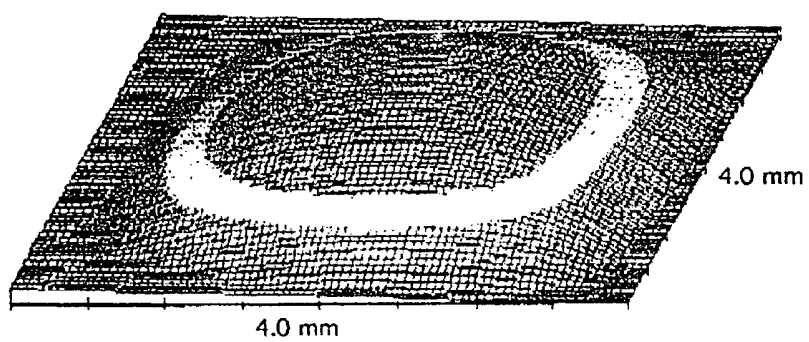


FIGURE 5

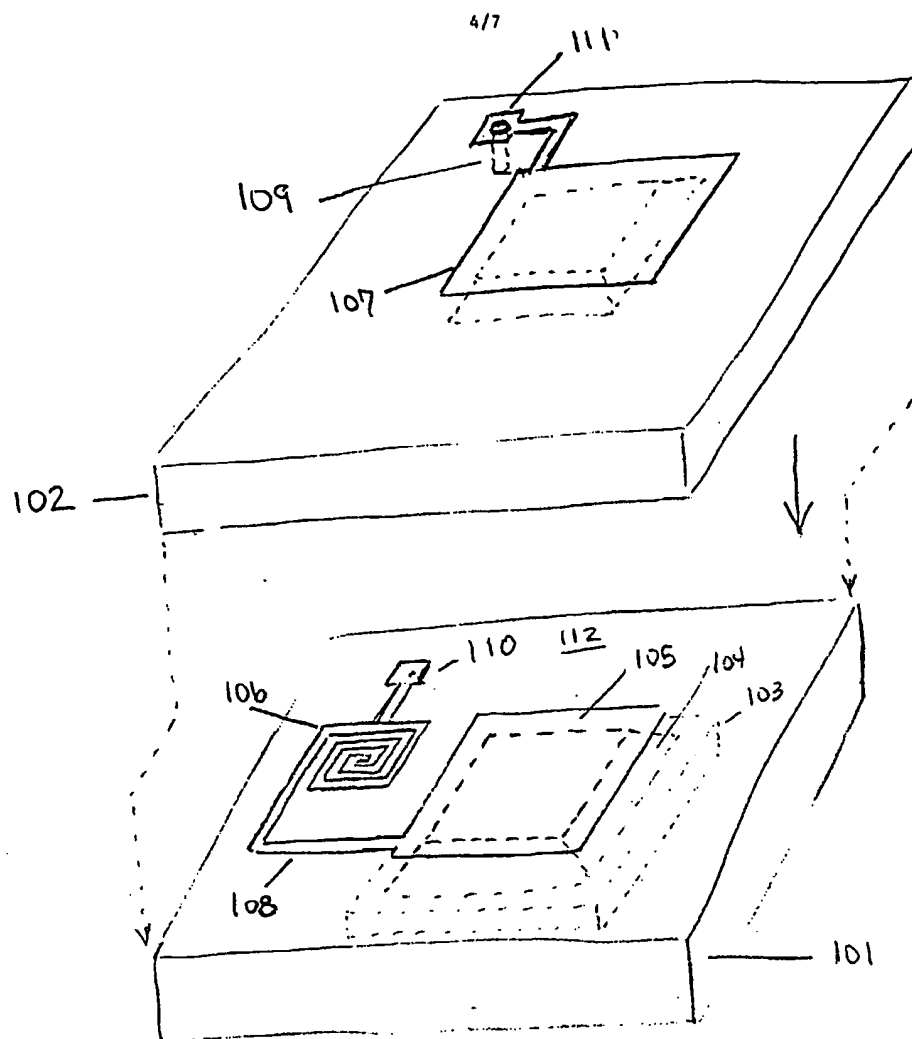


Fig 6

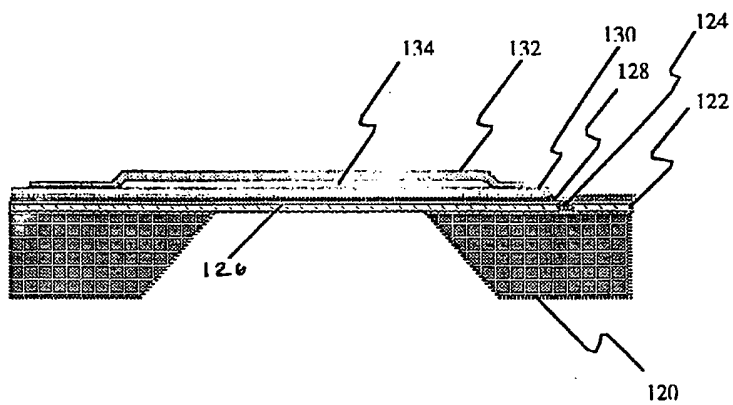


FIGURE 7

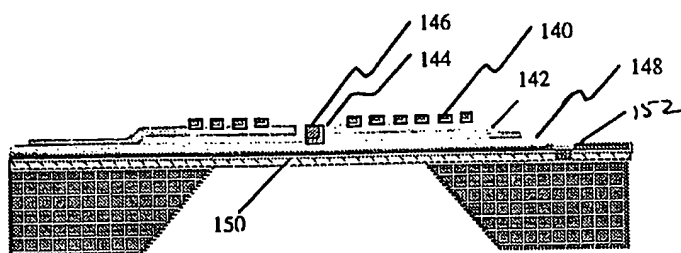


FIGURE 8

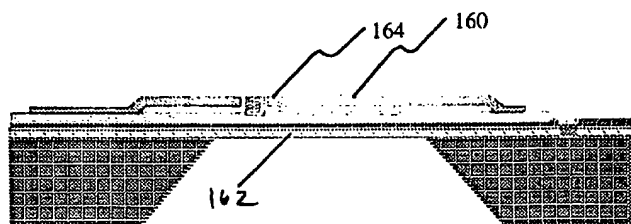


FIGURE 9



# INTERNATIONAL SEARCH REPORT

International Application No.  
PCT/US 99/23173

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61B5/00

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61B A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 28605 A (LIFECARE A/S) 2 July 1998 (1998-07-02) page 11, line 11 -page 14, line 7 figures 1-6 claims 1-4	1,27
A		2-7,15, 18,25
X	US 5 337 747 A (NEFTEL) 16 August 1994 (1994-08-16) column 3, line 45 -column 5, line 35 figures	1,27
A		2-7, 15-22, 24,25
	-/-	

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

18 February 2000

Date of mailing of the international search report

24/02/2000

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## INTERNATIONAL SEARCH REPORT

International Application No.  
PCT/US 99/23173

C. (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DE 195 01 159 A (EHWALD) 11 July 1996 (1996-07-11)  page 2, column 18, line 5 -page 35 figures	1-3,7,8, 15,16, 18,19, 21,24
A	US 5 062 841 A (SIEGEL) 5 November 1991 (1991-11-05) column 5, line 66 -column 6, line 63 figures 1A-1C	13-15
A	WO 98 29030 A (BIOSENSE INC.) 9 July 1998 (1998-07-09) page 19, line 7 -page 21, line 1 figures 6-7B	23-25
A	US 4 378 809 A (COSMAN) 5 April 1983 (1983-04-05) column 2, line 5 - line 46 column 3, line 64 -column 4, line 39 figure 1	26
P,X	GB 2 335 496 A (EGLISE) 22 September 1999 (1999-09-22) page 4, line 9 -page 10, line 11 figures 1-5	1,27

Form PCT/ISA210 (continuation of second sheet) (July 1992)

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No.

PCT/US 99/23173

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9828605 A	02-07-1998	NO 965566 A AU 7875098 A EP 0946863 A	24-06-1998 17-07-1998 06-10-1999
US 5337747 A	16-08-1994	FR 2652736 A AT 119006 T AU 638067 B AU 6510090 A CA 2044150 A,C DE 69017428 D DE 69017428 T DK 451233 T WO 9104704 A EP 0451233 A ES 2071115 T	12-04-1991 15-03-1995 17-06-1993 28-04-1991 07-04-1991 06-04-1995 21-09-1995 28-08-1995 18-04-1991 16-10-1991 16-06-1995
DE 19501159 A	11-07-1996	NONE	
US 5062841 A	05-11-1991	NONE	
WO 9829030 A	09-07-1998	AU 5338698 A CA 2247943 A EP 0904009 A	31-07-1998 09-07-1998 31-03-1999
US 4378809 A	05-04-1983	US 4281666 A	04-08-1981
GB 2335496 A	22-09-1999	AU 3043699 A WO 9948419 A	18-10-1999 30-09-1999

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